Power and precision in cancer radiotherapeutics

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Safety and Feasibility of Rhenium-186 NanoLiposome (\(^{186}\text{RNL}\)) in Recurrent Glioma: the ReSPECT™ Phase 1/2a Trial

Norman LaFrance, MD, ME, FACP, FACNP, FACNM - PRESENTER
Chief Medical Officer, SVP
Plus Therapeutics

Andrew Brenner, MD, PhD, UT Health San Antonio
Michael Youssef, MD, UT Southwestern
Ande Bao, PhD, Case Western Reserve University
William Phillips, MD, UT Health San Antonio
Marc Hedrick, MD Plus Therapeutics
Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Any statement in this document that is not a historical fact is a “forward-looking statements” within the meaning of Section 27A of the Securities Act & Section 21E of the Securities Exchange Act & are usually identified by the use of words such as “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “projects,” “seeks,” “should,” “will,” & variations of such words or similar expressions. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act & Section 21E of the Securities Exchange Act of 1934, as amended, & are making this statement for purposes of complying with those safe harbor provisions. These forward-looking statements reflect our current views about our plans, intentions, expectations, strategies & prospects, which are based on the information currently available to us & on assumptions we have made. Although we believe that our plans, intentions, expectations, strategies & prospects as reflected in or suggested by those forward-looking statements are reasonable, we can give no assurance that the plans, intentions, expectations or strategies will be attained or achieved. Furthermore, actual results may differ materially from those described in the forward-looking statements & will be affected by a variety of risks & factors that are beyond our control.

Risks & uncertainties for Plus include, but are not limited to: an inability or delay in obtaining required regulatory approvals for product candidates, which may result in unexpected cost expenditures; risks inherent in drug development in general; uncertainties in obtaining successful clinical results for product candidates & unexpected costs that may result therefrom; failure to realize any value of certain product candidates developed & being developed in light of inherent risks & difficulties involved in successfully bringing product candidates to market; inability to develop new product candidates & support existing products; the approval by the FDA & any other similar foreign regulatory authorities of other competing or superior products brought to market; risks resulting from unforeseen side effects; risk that the market for the combined company’s products may not be as large as expected; inability to obtain, maintain & enforce patents & other intellectual property rights or the unexpected costs associated with such enforcement or litigation; inability to obtain & maintain commercial manufacturing arrangements with third-party manufacturers or establish commercial scale manufacturing capabilities; loss of or diminished demand from one or more key customers or distributors; unexpected cost increases & pricing pressures; economic recession & its negative impact on customers, vendors or suppliers; uncertainties of cash flows, expenses & inability to meet working capital needs; & other risks & uncertainties detailed in the risk factors section of Plus’ Form 10-K & Forms 10-Q filed with the SEC, as well as other filings Plus makes with the SEC from time-to-time. Many of these factors that will determine actual results are beyond Plus’ ability to control or predict. Plus disclaims any obligation to update information contained in these forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.
Rare and Difficult-to-Treat Cancers

Responsible for Substantial Morbidity and Mortality Worldwide

+ Rare cancers represent 27% of all cancers; all pediatric cancers are rare
+ Rare cancers account for 25% of all cancer deaths; 5-year survival rate is lower for patients with a rare cancer than those with a more common cancer
+ Treatments for rare cancers are eligible for orphan drug designations

Central Nervous System Tumors

| Glioblastoma: Deadliest, most common brain cancer in adults |
| Leptomeningeal Metastases: Late complication in 5% of cancer patients |
| Pediatric Brain Cancer: 2nd most common type of cancer in children |

Sources: CBTRUS Statistical Report, NBTS, NCI
Radiation for GBM

Types of Radiation

External Beam Radiation

Internal Targeted Radiation

+ Up to a point, survival time for external beam radiation correlates with the total dose delivered.

+ The therapeutic window for external beam radiation is limited by increasing late normal tissue damage.

+ Due to the short path length and dose rates, intra-tumoral beta emitters have the potential to dramatically widen the therapeutic window, increase delivered dose, and extend survival time.
Direct Radiation Therapy with Rhenium-186

+ Rhenium-186 (Re-186, 186Re)
+ 89.3-hour half-life (3.72 days)
+ Beta energy: 1077 keV (71%), 939 keV (22%)
+ Gamma energy: 137 keV (9%)
+ Max. penetration in tissue: 4.5 mm (average 1.1 mm)

**Absorbed Radiation and Recurrent GBM**

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>DS DNA BREAKS</th>
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</thead>
<tbody>
<tr>
<td>EBRT (35 Gy)</td>
<td>700-1,400</td>
</tr>
<tr>
<td>(^{186}\text{RNL} ) (600 Gy)</td>
<td>12,000-24,000</td>
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</tbody>
</table>
**186RNL: A NanoLiposomal Radiotherapeutic**

N,N-bis(2-mercaptoethyl)-N’,N’-diethyl-ethylenediamine (BMEDA)-chelated 186Rhenium encapsulated within lipid vesicles (nanoliposomes)

- **BMEDA is an SNS pattern ligand with a tridentate structure that has one nitrogen and three sulfur atoms. These three atoms donate electrons to 186Rhenium, resulting in a lipophilic complex in a neutral state.**

- **Nanoliposomes are composed of an 80-130 nm diameter lipid bilayer of distearoylphosphatidylcholine (DSPC) and cholesterol and confer drug delivery control on the chelated 186Rhenium**

- **186Rhenium is an ideal radioisotope for therapy with imaging capabilities (SPECT), safety similar to 131I, and penetration in tissue averaging 1.1 mm**

- **186RNL manufactured under GMP**
Liposomal encapsulation fundamentally changes both the retention within the tumor and the dispersion of the drug product.

- Intracranial administration of 1, 3.5, or 6 mCi $^{186}$RNL produced no significant pathologic changes at 24 hours or 14 days.

- Highest absorbed dose was 360 Gy.

- Based on these data, the no adverse effect limit (NOAEL), as related to brain pathology, was determined to be an absorbed dose of 360 Gy.
ReSPECT-GBM Phase 1/2a Trial

Direct $^{186}$RNL Infusion By Convection Enhanced Delivery

+ Multi-center, sequential cohort, open-label, volume and dose finding study of the safety, tolerability, and distribution of $^{186}$RNL given by convection-enhanced delivery to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment
+ Phase 1 Dose Escalation Study
+ Phase 2 Efficacy Study
+ Supported by a National Institutes of Health (NIH)
+ 5 Sites

Convection-Enhanced Delivery of $^{186}$RNL Direct to the Brain Tumor

Convection Enhanced Delivery: A technique that generates a pressure gradient to deliver therapeutics through the interstitial spaces of the CNS

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[Logos and affiliations]
ReSPECT-GBM Phase 1/2a Trial

Inclusion / Exclusion Criteria

+ No prior bevacizumab (excluded from Cohort 5 onward)
+ Progression by RANO criteria following both standard combined modality treatment with radiation and temozolomide chemotherapy
+ Patients who receive treatment with antiepileptic medications must have a 2-week history of stable dose of antiepileptic without seizures prior to dosing
+ Patients with corticosteroid requirements to control cerebral edema must be maintained at a stable or decreasing dose for a minimum of two weeks without progression of clinical symptoms
+ A volume of enhancing tumor which falls within the treatment field volume being evaluated in the respective cohort
+ Restricted to glioblastoma from Cohort 6 forward (1 patient with AO and 1 with AA in early cohorts)
+ Standard organ function requirements
+ ECOG 0-2
ReSPECT-GBM Phase 1/2a Trial

Treatment Planning – MRI-Guided Catheter Placement for $^{186}$RLN Infusion by CED
### ReSPECT-GBM Phase 1/2a Trial

#### Phase 1 Dose Escalation

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Infused Volume (mL)</th>
<th>Total $^{186}$ RNL Activity</th>
<th>Concentration ($^{186}$ RNL/mCi/mL)</th>
<th>Average Absorbed Dose (Gy)</th>
<th>Status</th>
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<tbody>
<tr>
<td>1</td>
<td>0.66</td>
<td>1.0</td>
<td>1.5</td>
<td>198</td>
<td>Enrolling</td>
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<tr>
<td>2</td>
<td>1.32</td>
<td>2.0</td>
<td>1.5</td>
<td>122</td>
<td>Cohort 8 (n=24 subjects)</td>
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<tr>
<td>3</td>
<td>2.64</td>
<td>4.0</td>
<td>1.5</td>
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<td>4</td>
<td>5.28</td>
<td>8.0</td>
<td>1.5</td>
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<td>5</td>
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<td>2.5</td>
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<tr>
<td>6a</td>
<td>8.80</td>
<td>22.3</td>
<td>2.5</td>
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<tr>
<td>6b*</td>
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<td>22.3</td>
<td>2.5</td>
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<td>7</td>
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<td>31.2</td>
<td>2.5</td>
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<td>8</td>
<td>16.34</td>
<td>41.5</td>
<td>2.5</td>
<td>TBD</td>
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</table>

*Cohort 6b utilized the same volume and dose as Cohort 6a but with an increase in maximum flow rate to 20 microliters/minute.*
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-014

+ Tumor volume was 6.5 mL and tumor coverage was >90%
+ Absorbed dose delivered to tumor was 419 Gy
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-014

- MRI scans revealed an initial increase in size which peaked at Day 118, with some associated edema, followed by tumor shrinkage out to at least Day 362
- Patient survival >950 days
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-017

+ Tumor volume was 18.8 mL and tumor coverage was 87%
+ Absorbed dose delivered to tumor was 336 Gy
ReSPECT-GBM Phase 1/2a Trial
Phase 1 Dose Escalation – Subject 01-017

Pre-Treatment

Day 56

Tumor response

Perfusion Change
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – No Significant Extracranial Exposure
ReSPECT-GBM Phase 1/2a Trial
Phase 1 Dose Escalation – Coverage Correlates with Response
A statistically significant overall survival benefit in therapeutic doses (>100 Gy) vs. subtherapeutic (p = 0.002)

In cohorts 5-7 (higher volumes and doses), therapeutic dose achieved in 80% of patients

Increasing drug volume and radiation correlate with improved overall survival
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Data (N=23)

+ By comparison, median overall survival of 32.1 weeks reported in 8 study meta-analysis of 694 recurrent GBM patients treated with bevacizumab monotherapy
+ > 100 Gy: 3 patients remain alive, none < 100 Gy
ReSPECT-GBM Phase 1/2a Trial

Summary

+ **Safety**
  + Well tolerated, no dose limiting toxicities
+ **Delivery and Imaging**
  + No dosing failures
  + Single administration- up to 20x absorbed dose vs. EBRT (maximum 740 Gy vs. 35 Gy)
  + SPECT/CT- reliable real-time visualization and dosimetry
+ **Survival**
  + A statistically significant OS benefit in therapeutic doses (>100 Gy) vs. subtherapeutic (p = 0.002).
  + In cohorts 5-7 (higher volumes and doses), therapeutic dose achieved in 80% of patients.
  + Increasing drug volume and radiation correlate with improved OS
+ **Going Forward**
  + Continued Phase 1 dose escalation into Cohort 8
  + Phase 2 commencing with 22.3mCi in 8.8mL for GBM ≤20 cm³ in total volume
  + Approved Retreatment protocol commencing
  + Peds IND submission (Q4 2022, A Phase 1/2a Trial to Determine the Maximum Tolerated Dose, Safety, and Tolerability of Rhenium-186 Nanoliposome (¹⁸⁶RNL) Delivered via Convection Enhanced Delivery (CED) in Supratentorial Recurrent, Refractory, or Progressive Pediatric Ependymoma and High-Grade Glioma (HGG))
  + Multi-dose protocol in preparation (Q1 2023)
THANK YOU

+ Andrew Brenner, MD, PhD, UT Health San Antonio
+ Michael Youssef, MD, UT Southwestern
+ Ande Bao, PhD, Case Western Reserve University
+ William Phillips, MD, UT Health San Antonio
+ Marc Hedrick, MD, Plus Therapeutics
+ Melissa Moore, PhD, Plus Therapeutics
+ Our patients and their families

For more information on how to become involved with this trial, please contact:

Norman LaFrance, MD, ME, FACP, FACNP, FACNM
nlafrance@plustherapeutics.com